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Original article

## Depressive symptoms, insulin sensitivity and insulin secretion in the RISC cohort study

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### Abstract

**Aim.** – This study explored the association of depressive symptoms with indices of insulin sensitivity and insulin secretion in a cohort of non-diabetic men and women aged 30 to 64 years.

**Methods.** – The study population was derived from the 3-year follow-up of the Relationship between Insulin Sensitivity and Cardiovascular Disease Risk (RISC) study. Presence of significant depressive symptoms was defined as a Center for Epidemiologic Studies Depression Scale (CES-D) score  $\geq 16$ . Standard oral glucose tolerance tests were performed. Insulin sensitivity was assessed with the oral glucose insulin sensitivity (OGIS) index. Insulin secretion was estimated using three model-based parameters of insulin secretion (beta-cell glucose sensitivity, the potentiation factor ratio, and beta-cell rate sensitivity).

**Results.** – A total of 162 out of 1027 participants (16%) had significant depressive symptoms. Having significant depressive symptoms was not related to either OGIS [standardized beta ( $\beta$ )  $-0.033$ ;  $P=0.24$ ] or beta-cell glucose sensitivity ( $\beta$   $-0.007$ ;  $P=0.82$ ). Significant depressive symptoms were related to decreased beta-cell rate sensitivity (odds ratio for significant depressive symptoms of the lowest vs. highest quartile of beta-cell rate sensitivity was 2.04;  $P=0.01$ ). Also, significant depressive symptoms were associated with a statistically significant decrease in the potentiation factor ratio in unadjusted models, but not in the fully adjusted model.

**Conclusion.** – Depressive symptoms were not related to insulin sensitivity and tended to be weakly associated to some parameters of insulin secretion in non-diabetic individuals. Prospective studies are needed to study the temporal association between depression and insulin secretion.  
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**Keywords:** Depression; Diabetes; Insulin sensitivity; Insulin secretion

### Résumé

Présence de symptômes de dépression, insulinosensibilité et insulinosécrétion dans l'étude de cohorte RISC.

**But.** – Explorer l'association entre la présence de symptômes dépressifs et des indices de l'insulinosensibilité et de l'insulinosécrétion dans une cohorte d'hommes et de femmes non diabétiques, âgés de 30 à 64 ans.

**Méthodes.** – La population étudiée est issue du suivi à trois ans de la cohorte Relationship between Insulin sensitivity and Cardiovascular risk (RISC). La présence de symptômes dépressifs significatifs a été définie par un Center for Epidemiologic Studies Depression Scale (CES-D) avec un score supérieur ou égale à 16. Un test d'hyperglycémie provoquée par voie orale a été réalisé, l'insulinosensibilité a été évaluée par l'indice Oral

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Glucose Insulin sensitivity (OGIS) et l'insulinosécrétion a été estimée à partir de trois modèles (sensibilité des cellules bêta au glucose, facteur de potentialisation, et sensibilité des cellules bêta).

**Résultats.** – Cent soixante-deux des 1027 participants (16 %) présentaient des symptômes dépressifs significatifs. La présence de symptômes dépressifs significatifs n'était pas liée à l'insulinosensibilité déterminée par l'indice OGIS (bêta standardisé [ $\beta$ ]  $-0,033$ ,  $P=0,24$ ), ni à la sensibilité des cellules bêta au glucose ( $\beta -0,007$ ,  $P=0,82$ ). La présence de symptômes dépressifs significatifs était liée à une diminution de la sensibilité des cellules bêta (l'*odds ratio* du quartile le plus élevé par rapport au quartile inférieur de la sensibilité des cellules bêta pour la présence de symptômes dépressifs importants OR 2,04,  $P=0,01$ ). Enfin, la présence de symptômes dépressifs importants était associée à une diminution statistiquement significative du facteur de potentialisation dans le modèle non ajusté, mais non dans le modèle ajusté.

**Conclusion.** – La présence de symptômes de dépression n'est pas liée à l'insulinosensibilité, mais est faiblement liée à certains paramètres de l'insulinosécrétion chez les personnes non diabétiques. Des études prospectives sont nécessaires pour étudier l'association temporelle entre la dépression et la sécrétion de l'insuline.

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**Mots clés :** Dépression ; Diabète ; Sensibilité à l'insuline ; Sécrétion de l'insuline

## 1. Introduction

Depression is commonly seen in diabetes. A meta-analysis showed that the prevalence of depression (measured as significant depressive symptoms or clinical depression) is almost doubled in individuals with type 2 diabetes compared with those without diabetes (17.6% vs. 9.8%) [1]. Depression is frequently considered a condition that results from the daily burden of having diabetes. However, other studies show that depression in turn is an independent risk factor for the development of type 2 diabetes [2]. Recently, Mezuk et al. [3] showed in their meta-analysis that depression was associated with a 60% increased risk of future type 2 diabetes, while Nouwen et al. [4] showed that type 2 diabetes was related to a 24% increased risk of future depression. Several interconnected mechanisms have been proposed by which depression could accelerate the onset of type 2 diabetes, including increased hypothalamic–pituitary–adrenal (HPA) axis activity, increased low-grade inflammation [5,6], impaired intake or metabolism of omega-3 polyunsaturated fatty acids [7,8] and visceral obesity [9]. In addition, it has been suggested that depression-associated insulin resistance (DAIR) could account for the increased risk of type 2 diabetes related to depression [10]. Several studies have shown that depressive symptoms are associated with greater insulin resistance [11–15]. Recently, it was reported that young adults with a depressive disorder formally diagnosed by the Composite International Diagnostic Interview (CIDI) were more insulin-resistant [16]. However, other studies have not observed a significant relationship between depressive symptoms and insulin resistance or even found a negative relationship [17–20].

Both insulin sensitivity and insulin secretion are independent predictors of worsening glucose tolerance, which can lead to diabetes [21]. In addition to reduced insulin sensitivity, reduced insulin secretion by the pancreatic beta cells may also explain part of the increased diabetes risk associated with depression. Although several studies have focused on the relationship of depression with insulin sensitivity, less is known of its relationship with insulin secretion. Holt et al. observed no significant associations between depressive symptoms and homeostatic model assessment for insulin secretion (HOMA-B) in a population-based study [22]. In another study, the acute insulin response (AIR), an indicator for early insulin secretion,

was increased in patients with depression compared with controls [23].

To further improve our knowledge of the mechanisms that link depression and diabetes incidence, the associations between depressive symptoms and indices of (1) insulin sensitivity and (2) insulin secretion were examined in a large, relatively healthy, European cohort of men and women aged 30 to 64 years.

## 2. Methods

The study population was derived from the 3-year follow-up of the Relationship between Insulin sensitivity and Cardiovascular Disease Risk (RISC) study, a prospective observational cohort study of relatively healthy individuals. The design, protocol and purpose of the RISC study have been described elsewhere [24]. Briefly, 1326 clinically healthy Caucasian people aged 29 to 61 years were recruited at 19 centres in 14 European countries. Each centre had its local ethics committee approval and all participants gave their written informed consent to participate. Exclusion criteria were the presence of chronic diseases and overt cardiovascular diseases and/or treatment for obesity, hypertension, lipid disorders and diabetes. In addition, those with blood pressure  $\geq 140/90$  mmHg, total cholesterol  $\geq 7.8$  mmol/L, triglycerides  $\geq 4.6$  mmol/L, fasting glucose  $\geq 7.0$  mmol/L and 2-h glucose  $\geq 11.1$  mmol/L were excluded. Baseline assessments were collected between 2002 and 2005. After 3 years, follow-up measurements were taken in 1085 participants. Depressive symptoms were first assessed at this time point. Cross-sectional data from the 3-year follow-up were used in the present report.

### 2.1. Protocol

At the 3-year follow-up, demographic and lifestyle characteristics were assessed by questionnaire. In addition, participants were invited to the study centre for anthropometric measurements and blood sampling. Participants underwent a 75 g oral glucose tolerance test (OGTT) after an overnight fast. Blood samples were taken before and during the test at 0, 30, 60, 90 and 120 min. Patients who self-reported the use of medication for diabetes were excluded from the present analyses ( $n=5$ ), as this could influence glucose and insulin levels. In addition, the

number of psychoactive drugs being taken by each participant was recorded.

## 2.2. Depressive symptoms

At the 3-year follow-up, depressive symptoms were assessed by the Centre for Epidemiologic Studies Depression scale (CES-D) [25], a validated 20-item self-reported depression scale that has good psychometric properties across several populations [25,26]. Individuals completed the CES-D in their native language. Items in the scale refer to the frequency of depressive symptoms over the last 7 days. The total possible score ranges from 0 to 60, with higher scores reflecting more depressive symptoms. The CES-D cut-off score of  $\geq 16$  was used to distinguish those with significant depressive symptoms from the non-depressed persons [25]. For participants who were missing four or fewer items ( $n=68$ ), the missing scores were assigned the value of the mean score of the completed items for that participant.

## 2.3. Insulin sensitivity

As a measure of insulin sensitivity, the oral glucose insulin sensitivity (OGIS) index was calculated. This model-based method for assessing insulin sensitivity uses OGTT-derived glucose and insulin concentrations at 0, 90 and 120 min [27]. The OGIS is a dynamic surrogate measure of insulin sensitivity that has been validated against euglycaemic clamp data (Pearson's correlation  $r=0.7$ ) [27]. Furthermore, as a secondary outcome, the inverse of fasting insulin ( $1/\text{fasting insulin}$ ) was also used to assess insulin sensitivity. In healthy individuals,  $1/\text{fasting insulin}$  is a well-accepted proxy for insulin sensitivity [28].

## 2.4. Insulin secretion

While insulin sensitivity can reliably be estimated *in vivo*, measurement of insulin secretion is more complicated. It has been advocated that beta-cell functioning cannot be reduced to a single value, but should instead be assessed by multiple model-based insulin secretion parameters [29]. Therefore, three model-based parameters of beta-cell function (beta-cell glucose sensitivity, the potentiation factor ratio and beta-cell rate sensitivity) were calculated according to a previously described model [30,31]. This model describes insulin secretion as the sum of two components.

The first component represents the dependence of insulin secretion on absolute glucose concentration at any time point during the OGTT through a dose–response function. The variable that describes this dose–response relationship is termed “beta-cell glucose sensitivity” and is defined as the mean slope over the observed glucose range. The dose–response relationship is modulated by the potentiation factor, which accounts for the higher insulin secretion during the descending phase of hyperglycaemia than during the ascending phase with the same glucose concentration during acute stimulation. It is set as a positive function of time and to average one during the OGTT. Therefore, it represents the relative potentiation of the insulin

secretion response to glucose. The potentiation parameter used in the present analysis is the ratio of the potentiation factor at the end of the 2-h OGTT to the one at the start.

The second component of insulin secretion represents the dynamic dependence of insulin secretion on the rate of change in glucose concentration. This component is termed “beta-cell rate sensitivity” and represents early insulin release.

As a secondary classical outcome for insulin secretion, the insulinogenic index was determined as the ratio of the increment in insulin concentration divided by the increment in glucose concentration during the first 30 min of the OGTT:  $(\text{Insulin } 30 \text{ min} - \text{Insulin } 0 \text{ min})/(\text{Glucose } 30 \text{ min} - \text{Glucose } 0 \text{ min})$  [32].

## 2.5. Covariates

Gender and age were derived from the demographic questionnaires. The centre of recruitment was registered for each participant. Smoking status (never, smoker, ex-smoker) and alcohol intake (g/day) were assessed through items on the lifestyle questionnaire. Physical activity was assessed with the full version of the International Physical Activity Questionnaire (IPAQ), which has been validated for international studies [33]. Its questions refer to physical activity over the past 7 days. Using the scoring system available online at [www.ipaq.ki.se](http://www.ipaq.ki.se), the level of physical activity for each participant was classified as either inactive, minimally active or health-enhancing.

## 2.6. Analytical methods

Blood samples were separated into plasma and serum, divided into aliquots and stored at  $-80^\circ\text{C}$  for glucose, insulin and C-peptide determination. Samples were transported on dry ice at prearranged intervals to central laboratories. Plasma glucose was measured using the glucose-oxidase technique. Serum insulin was measured by a specific time-resolved immunofluorometric assay (AutoDELFIA insulin kit, Wallac Oy, Turku, Finland), with the following assay characteristics: sensitivity 1–2 pmol/L; within-assay variation 5%; and between-assay variation 5%.

## 2.7. Statistical analysis

The demographic and clinical characteristics were compared between participants with significant depressive symptoms and those without significant symptoms. Continuous variables were compared using independent *t* tests and categorical variables using  $\chi^2$  tests. Linear regression analyses were performed with significant depressive symptoms as predictors and the two insulin sensitivity measures (OGIS and logarithmically transformed  $1/\text{fasting insulin}$ ) as outcome variables. Potential confounders (gender, age, centre) and potential behavioral mediators (smoking status, alcohol intake and physical activity) were added to the linear regression model in a stepwise approach. Likewise, linear regression analyses were performed with the logarithmically transformed indices of insulin secretion (beta-cell glucose sensitivity, potentiation factor ratio, beta-cell rate sensitivity and insulinogenic index) as outcome variables. In

Table 1

Characteristics of depressed versus non-depressed participants in the 3-year follow-up of the RISC study ( $n = 1027$ ).

	Non-depressed ( $n = 865$ )	Depressed ( $n = 162$ )	<i>P</i>
Women	446/865 (51.6%)	113/162 (69.8%)	< 0.001
Smoking status			
Never	408/857 (47.6%)	64/158 (40.5%)	< 0.001
Smoker	162/857 (18.9%)	52/158 (32.9%)	
Ex-smoker	287/857 (33.5%)	42/158 (26.6%)	
IPAQ score			0.034
Inactive	190/862 (22.0%)	42/157 (26.8%)	0.230
Minimally active	325/862 (37.7%)	69/157 (43.9%)	
Health-enhancing physical activity	347/862 (40.3%)	46/157 (29.3%)	
IFG or IGT <sup>a</sup>	142/850 (16.7%)	33/160 (20.6%)	0.230
Use of psychoactive drugs	34/819 (4.2%)	21/153 (13.7%)	< 0.001
	Mean (SD)	Mean (SD)	<i>P</i>
Age (years)	47.7 (8.3)	48.9 (7.9)	0.098
Body mass index (kg/m <sup>2</sup> )	25.7 (4.1)	26.0 (4.4)	0.406
Systolic blood pressure (mmHg)	121 (15)	119 (15)	0.172
	Median (IR)	Median (IR)	<i>P</i>
Alcohol intake (g/week)	53 (15–105)	35 (0–78)	0.004 <sup>b</sup>
OGIS (mL min <sup>-1</sup> kg lean body mass <sup>-1</sup> )	10.9 (9.2–12.8)	10.8 (9.4–12.8)	0.406 <sup>b</sup>
1/fasting insulin (pmol L <sup>-1</sup> )	0.032 (0.022–0.045)	0.032 (0.023–0.046)	0.599 <sup>b</sup>
Beta-cell glucose sensitivity (pmol min <sup>-1</sup> m <sup>-2</sup> mM <sup>-1</sup> )	111.3 (80.6–159.7)	107.6 (72.6–154.6)	0.357 <sup>b</sup>
Beta-cell rate sensitivity (pmol m <sup>-2</sup> mM <sup>-1</sup> )	2.96 (2.59–3.21)	2.87 (2.43–3.11)	0.012 <sup>b</sup>
Potential factor ratio	1.68 (1.17–2.46)	1.50 (1.11–2.07)	0.045 <sup>b</sup>
Insulinogenic index	76.9 (49.6–117.3)	67.5 (42.4–106.6)	0.021 <sup>b</sup>

IPAQ: international physical activity questionnaire; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; IR: interquartile range; OGIS: oral glucose insulin sensitivity index.

<sup>a</sup> IFG defined as fasting plasma glucose (FPG)  $\geq 6.1$  mmol/L and < 7.0 mmol/L; IGT defined as 2-h plasma glucose  $\geq 7.8$  mmol/L and < 11.1 mmol/L.

<sup>b</sup> Mann–Whitney U test.

addition to the previously stated covariates, 1/fasting insulin was added as a covariate when the insulinogenic index was studied to adjust for the prevailing level of insulin sensitivity. The other reported insulin-secretion variables are considered to be independent of insulin sensitivity [34], so no adjustments were made for insulin sensitivity to those indices. For all linear regression models except beta-cell rate sensitivity, assumptions regarding normality of residuals were met. For this reason, rate sensitivity was categorized into quartiles, and multinomial regression analyses was used with the lowest quartile as the reference category. In the analysis with rate sensitivity, there was no adjustment for centre due to the risk of statistical over fitting.

In addition, several sensitivity analyses were conducted. The above-mentioned linear regression analyses were repeated:

- using continuous CES-D scores instead of the binary CES-D cut-off;
- after excluding participants who used psychoactive drugs and;
- after excluding participants with fasting plasma glucose  $\geq 7.0$  mmol/L and/or 2-h plasma glucose  $\geq 11.1$  mmol/L.

Although such raised values indicate diabetes, these were only single assessments of plasma glucose, whereas elevated levels should be confirmed on multiple occasions before diagnosing diabetes [35]. Furthermore, to investigate the possibility

of a non-linear relationship between depressive symptoms and insulin sensitivity/secretion, gender-stratified quartiles were constructed for each insulin sensitivity/secretion parameter. These quartiles were then combined and used to compare the prevalence of significant depressive symptoms in each quartile. Pearson's Chi<sup>2</sup> tests and the Mantel–Haenszel linear-by-linear association test were used to test differences in the prevalence of depression between quartiles. All analyses were performed using PASW version 17.0 statistics software. A two-tailed *P* value < 0.05 was considered statistically significant.

### 3. Results

Of the 1027 subjects who completed the CES-D, 162 (16%) were identified as having significant depressive symptoms and 865 (84%) were non-depressed. The demographic, behavioral and medical characteristics of the sample are presented in Table 1, stratified by depressive status. Those with significant depressive symptoms more often were women, smokers, less physically active and consumed less alcohol per week compared with the non-depressed subjects. No differences were observed with regard to age, body mass index and systolic blood pressure between participants with significant depressive symptoms and those without.

Table 2 shows the results of the linear regression analysis with the OGIS and log 1/fasting insulin. There was no statistically



Table 2  
Linear regression analyses of the association of depression with two insulin sensitivity measures: oral glucose insulin sensitivity (OGIS) index and 1/fasting insulin.

Outcome	Depression	B <sup>a</sup> (95% CI)	β	P
OGIS (n = 937)	Unadjusted	0.273 (−0.229, 0.775)	0.035	0.286
	Model 1	−0.232 (−0.685, 0.221)	−0.030	0.315
	Model 2	−0.188 (−0.628, 0.251)	−0.024	0.401
	Model 3	−0.286 (−0.717, 0.145)	−0.037	0.194
	Model 4	−0.300 (−0.736, 0.135)	−0.038	0.176
	Model 5	−0.301 (−0.737, 0.136)	−0.038	0.177
	Model 6	−0.262 (−0.695, 0.172)	−0.033	0.237
1/fasting insulin <sup>b</sup> (n = 954)	Unadjusted	0.008 (−0.033, 0.050)	0.013	0.692
	Model 1	−0.003 (−0.045, 0.038)	−0.005	0.881
	Model 2	−0.003 (−0.044, 0.039)	−0.004	0.906
	Model 3	0.007 (−0.036, 0.049)	0.010	0.762
	Model 4	0 (−0.042, 0.043)	0	0.997
	Model 5	−0.002 (−0.044, 0.041)	−0.003	0.938
	Model 6	0.003 (−0.039, 0.046)	0.005	0.874

Model 1: adjusted for gender; Model 2: adjusted for gender and age; Model 3: adjusted for gender, age and centre; Model 4: adjusted for gender, age, centre and smoking status; Model 5: adjusted for gender, age, centre, smoking status and alcohol intake; Model 6: adjusted for gender, age, centre, smoking status, alcohol intake and physical activity.

<sup>a</sup> Unstandardized regression coefficient (β is the standardized regression coefficient).

<sup>b</sup> Logarithmically transformed before linear regression analysis.

significant association between the presence of depressive symptoms and these two surrogates of insulin sensitivity.

Table 3 presents the results of the regression analysis including insulin-secretion parameters. Depressive symptoms were not related to the beta-cell glucose sensitivity component. However, significant depressive symptoms were statistically significantly related to the potentiation factor ratio although, after adjusting for potential confounders (gender, age and centre), this association was no longer significant. The addition of the potential mediators also had no further effects on this association.

As for beta-cell rate sensitivity, multinomial regression analyses showed that subjects with significant depressive symptoms were more likely to be in the lowest quartile of beta-cell rate sensitivity compared with the highest quartile [odds ratio (OR): 2.04, 95% CI: 1.16–3.60;  $P = 0.01$ , fully adjusted analyses]. This suggests that the beta-cell rate sensitivity is lower in depressed people. As shown in Table 3, the presence of significant depressive symptoms appeared to be related to a lower insulinogenic index in unadjusted analyses. However, after adjusting for the confounders, this association was no longer significant.

### 3.1. Sensitivity analyses

When the depression score was used instead of the binary variable for depression, the associations between depression and insulin sensitivity/secretion were comparable except for the association with OGIS. The CES-D score was weakly related to a lower OGIS (beta = −0.06;  $P = 0.037$ ). Also, excluding participants who used psychoactive drugs ( $n = 56$ ) and those with fasting plasma glucose  $\geq 7.0$  mmol/L and/or 2-h plasma glucose  $\geq 11.1$  mmol/L ( $n = 14$ ) from the present analyses did not materially affect the associations between significant depressive symptoms and insulin sensitivity and secretion.

Fig. 1 shows the prevalence of significant depressive symptoms by quartiles of each primary outcome parameter studied after adjusting for gender. The graphs show that the prevalence of significant depressive symptoms did not differ across quartiles of OGIS and beta-cell glucose sensitivity. On the other hand, the prevalence of depressive symptoms was significantly lower in the highest quartiles of potentiation factor ratio and beta-cell rate sensitivity.

## 4. Discussion

In this relatively healthy sample of men and women aged 30 to 64 years, the presence of significant depressive symptoms was not related to measures of insulin sensitivity, but tended to be weakly related to some indices of insulin secretion. Depressive symptoms were related to a slightly reduced first-phase insulin response during the OGTT, as indicated by the insulinogenic index, although this association disappeared after adjusting for potential confounders. In addition, depressive symptoms were also related to lower rate sensitivity in response to glucose and a decreased potentiation factor ratio.

In the present study, no significant association was observed between depressive symptoms and surrogate measures of insulin sensitivity. This is consistent with some studies [17,18,20], but contrary to others [11–16]. Furthermore, a recent meta-analysis could find no greater prevalence of depression in patients with impaired glucose metabolism (impaired fasting glucose and impaired glucose tolerance combined) compared with people with normal glucose metabolism [36]. One explanation for the lack of association in our study could be related to our sample, which comprised relatively young Caucasians who may have had more adequate levels of insulin sensitivity and secretion than those included in other studies. Caucasians are known to

Table 3

Linear regression analyses of the association of depression with insulin-secretion parameters.

Outcome	Depression	B <sup>b</sup> (95% CI)	β	P
Beta-cell glucose sensitivity <sup>a</sup> (n = 925)				
	Unadjusted	−0.021 (−0.070, 0.029)	−0.027	0.416
	Model 1	−0.032 (−0.082, 0.017)	−0.042	0.203
	Model 2	−0.030 (−0.080, 0.020)	−0.039	0.234
	Model 3	−0.006 (−0.053, 0.041)	−0.008	0.793
	Model 4	−0.004 (−0.051, 0.044)	−0.005	0.878
	Model 5	−0.004 (−0.052, 0.043)	−0.006	0.856
	Model 6	−0.006 (−0.053, 0.042)	−0.007	0.816
Potentiation factor ratio <sup>a</sup> (n = 925)				
	Unadjusted	−0.043 (−0.084, −0.001)	−0.066	0.045
	Model 1	−0.052 (−0.094, −0.010)	−0.080	0.015
	Model 2	−0.054 (−0.096, −0.012)	−0.084	0.011
	Model 3	−0.037 (−0.078, 0.003)	−0.058	0.070
	Model 4	−0.034 (−0.075, 0.006)	−0.053	0.097
	Model 5	−0.034 (−0.075, 0.006)	−0.053	0.096
	Model 6	−0.034 (−0.074, 0.007)	−0.052	0.105
Insulinogenic index <sup>a</sup> (n = 919)				
	Unadjusted	−0.059 (−0.114, −0.003)	−0.069	0.038
	Model 1	−0.066 (−0.122, −0.010)	−0.077	0.021
	Model 2	−0.063 (−0.118, −0.008)	−0.074	0.026
	Model 3	−0.044 (−0.100, 0.012)	−0.051	0.124
	Model 4	−0.036 (−0.092, 0.021)	−0.042	0.215
	Model 5	−0.034 (−0.090, 0.023)	−0.039	0.244
	Model 6	−0.037 (−0.094, 0.019)	−0.044	0.193
	Model 7	−0.039 (−0.093, 0.014)	−0.046	0.152

Model 1: adjusted for gender; Model 2: adjusted for gender and age; Model 3: adjusted for gender, age and centre; Model 4: adjusted for gender, age, centre and smoking status; Model 5: adjusted for gender, age, centre, smoking status and alcohol intake; Model 6: adjusted for gender, age, centre, smoking status, alcohol intake and physical activity; Model 7: adjusted for gender, age, centre, smoking status, alcohol intake, physical activity and 1/fasting insulin.

<sup>a</sup> Logarithmically transformed before linear regression analysis.

<sup>b</sup> Unstandardized regression coefficient (β is the standardized regression coefficient).

have a lower risk of glucose intolerance and diabetes compared with other ethnic groups [37].

Both insulin sensitivity and insulin secretion are predictors of changes in glucose tolerance [21]. Compared with assessment of insulin sensitivity, assessing beta-cell function and insulin secretion is relatively complex [29], as beta-cells have to adjust insulin release in an appropriate amount and time course in response to acute changes in plasma glucose concentrations. Our present study found that depressive symptoms were related to reduced early insulin-secretion levels, as indicated by a slightly lower insulinogenic index, and to reduced rate sensitivity. Reduced early insulin secretion is seen in diabetes patients [31]. Our observations are in contrast to the study of Okamura et al. [23], which showed that AIR was increased in patients with major depression compared with controls. In addition, they showed that AIR decreased after antidepressant therapy in patients with depression [23]. The reason for this discrepancy is unclear, but could be related to the use of different surrogates for early insulin secretion, and the study's particular design and sample population (patients diagnosed with major depressive disorder vs. those with increased depressive symptoms). Moreover, our study showed that depressive symptoms were related to reduced potentiation of insulin secretion. The potentiation factor comprises several potentiating mechanisms such as prolonged exposure to hyperglycaemia, non-glucose substrates, gastrointestinal hormones and neurotransmitters [38]. As with reduced early insulin

secretion, reduced potentiation is also seen in diabetes patients [31]. Thus, the observed relationship between depressive symptoms and markers of insulin secretion appears to be in the hypothetical diabetes related direction.

Nevertheless, as studies are sparse and conflicting, more and larger studies are needed to investigate how depressive symptoms relate to insulin secretion in specific subgroups of individuals.

Strengths of our study are its innovative character and the large number of participants from 14 European countries. The study also looked at the association between depressive symptoms and various components of beta-cell functioning and, thus, was a better reflection of the complexity of insulin secretion than the single parameters used in previous studies.

Our present study also had several limitations. First, surrogate measures were used for depression, and insulin sensitivity and secretion, as the gold-standard measures were not assessed during the 3-year follow-up. However, these validated indices are commonly used in epidemiological studies, as the gold standards are not always feasible. Second, our data were cross-sectional and, thus, no causal inferences could be made. Furthermore, it might be that only sustained elevated depressive symptoms are related to changes in insulin sensitivity and secretion. Future longitudinal studies are warranted to further explore the associations between depressive symptoms and insulin sensitivity and secretion. Third, whether adjusting for study centre is necessary

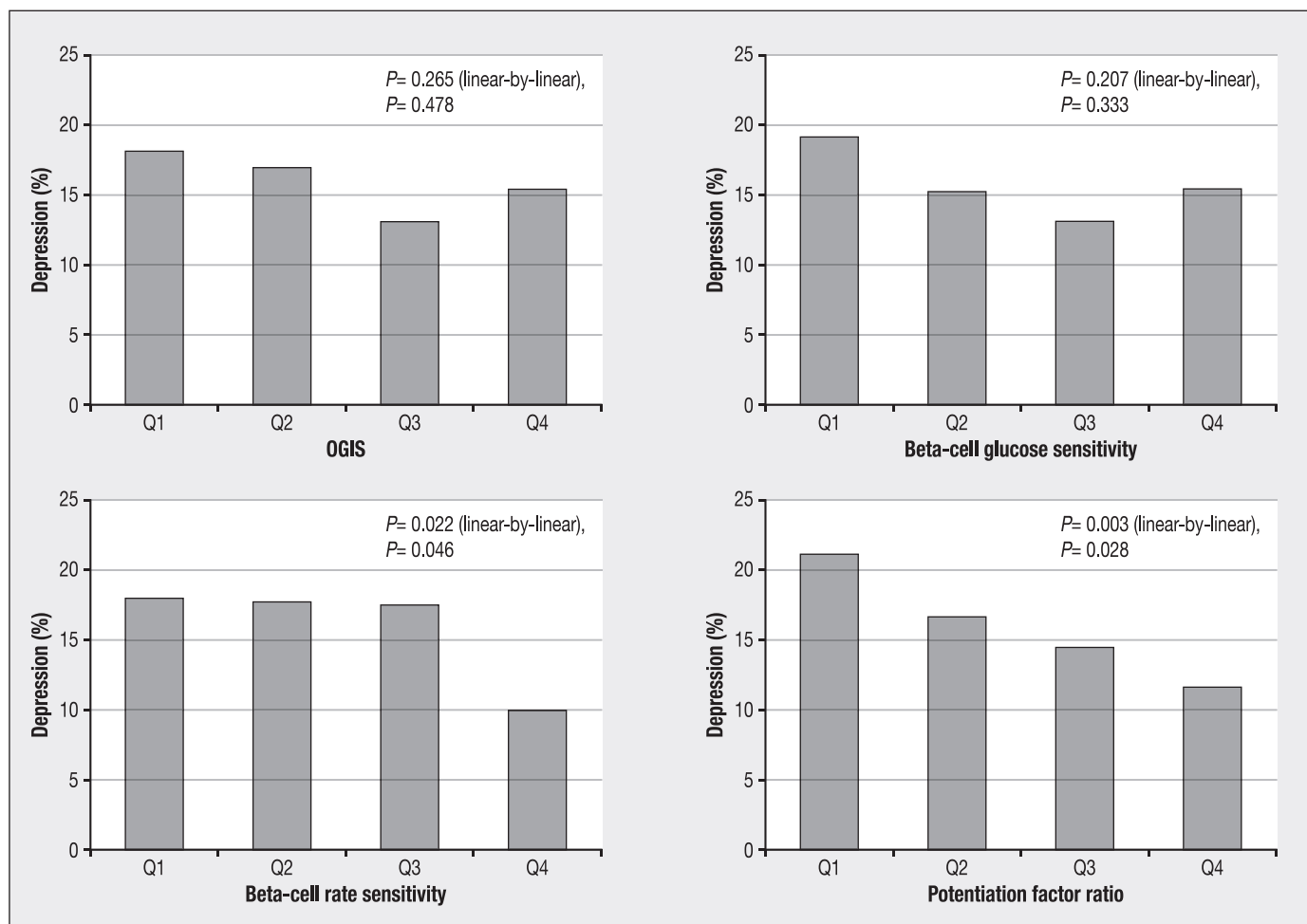


Fig. 1. Prevalence of elevated depressive symptoms for each quartile of OGIS (oral glucose insulin sensitivity index) and beta-cell glucose sensitivity, beta-cell rate sensitivity and potentiation factor ratio (insulin secretion). Q1–4: quartiles 1 (lowest values) to 4 (highest values); adjusted for gender; corresponding  $P$  values by Pearson's  $\chi^2$  tests ( $P$ ) and Mantel–Haenszel linear-by-linear association test ( $P$  linear-by-linear).

needs to be discussed, as it is likely that centres differ in measured and unmeasured characteristics despite using the same selection criteria for participants. However, although this may justify adjusting for centre in the analyses, it remains unclear as to what exactly this statistical adjustment means.

In conclusion, cross-sectional analyses in our large-scale multicentre cohort study did not demonstrate a significant association between elevated depressive symptoms and measures of insulin sensitivity. In this relatively healthy sample population, depressive symptoms tended to be related to reductions in some parameters of insulin secretion, although these associations were weak.

#### Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabet.2012.09.005>.

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